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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/275,883	03/25/1999	WOLFGANG A. RENNER	1700.0020001	1349

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EXAMINER	
SCHNIZER, RICHARD A	
ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 11/14/2002

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Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action

Application No.	Applicant(s)
09/275,883	Renner et al
Examiner	**Art Unit**
Richard Schnizer	1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED *Nov 4, 2002* FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid the abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

THE PERIOD FOR REPLY [check only a) or b)]

a) ☐ The period for reply expires _____ months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☒ A Notice of Appeal was filed on *Jan 4, 2002*. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☐ The proposed amendment(s) will not be entered because:

(a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

(b) ☐ they raise the issue of new matter (see NOTE below);

(c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

(d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: _____

3. ☐ Applicant's reply has overcome the following rejection(s):

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☒ The a) ☐ affidavit, b) ☐ exhibit, or c) ☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because:
See attached.

6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☒ For purposes of Appeal, the proposed amendment(s) a) ☐ will not be entered or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: *102*

Claim(s) objected to: _____

Claim(s) rejected: *75-78, 81-84, 86-101, 103, 105-107, and 109-145*

Claim(s) withdrawn from consideration: _____

8. ☐ The proposed drawing correction filed on _____ is a) ☐ approved or b) ☐ disapproved by the Examiner.

9. ☐ Note the attached Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____.

10. ☐ Other:

ADVISORY ACTION

Applicants request for reconsideration has been fully considered but does not place the application in condition for allowance.

Written Description

Applicant has amended the claims to require that mutations causing non-cytopathicity and temperature sensitivity of alphaviral replicases must occur in nonstructural proteins of the replicase. Applicant asserts that non-cytopathicity and temperature sensitivity may be conferred by mutations in genes other than NSP2 and NSP4, and notes that alphaviruses generally share a high degree of sequence homology.

The rejection is maintained for the reasons of record, i.e. the specification has failed to disclose what mutations are required to render any alphaviral replicase, other than the single disclosed example, both temperature sensitive and non-cytopathic, or what other mutations could confer this phenotype on the Sindbis virus polymerase. The state of the art of the prediction of protein function based on protein structure is not sufficiently advanced to predict *a priori* what mutations will confer temperature sensitivity or non-cytopathicity on a given replicase, so it falls to the specification to provide this information. One of skill in the art appreciates that a wide variety of alphaviral replicase is known in the art. In view of this recognized variety, and in view of the uncertainty associated with predicting which amino acid substitutions will confer temperature sensitivity and non-cytopathicity on a given polymerase, the disclosure of only a

single species is considered insufficient to convey to one of skill in the art that applicant was in possession of the claimed genus at the time of the invention.

The courts have found that merely describing the functional characteristics of a protein encoded by a particular nucleic acid is insufficient to adequately describe the genus of nucleic acids encoding that protein. A gene is a chemical compound, albeit a complex one, and it is well established in our law that conception of a chemical compound requires that the inventor be able to define it so as to distinguish it from other materials, and to describe how to obtain it. See Oka, 849 F.2d at 583, 7 USPQ2d at 1171. Conception does not occur unless one has a mental picture of the structure of the chemical, or is able to define it by its method of preparation, its physical or chemical properties, or whatever characteristics sufficiently distinguish it. It is not sufficient to define it solely by its principal biological property, e.g., non-cytopathic, temperature-sensitive RNA-dependent RNA polymerase, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property. When an inventor is unable to envision the detailed constitution of a gene so as to distinguish it from other materials, conception has not been achieved until reduction to practice has occurred, i.e., until after the gene has been isolated. Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016, 1021 (Fed. Cir. 1991). The instant application does not provide a written description that would allow one of skill in the art to immediately envisage the specific structure for Sindbis virus non-cytopathic, temperature-sensitive RNA-dependent RNA polymerases, or for the broader genus of alphaviral non-cytopathic, temperature-sensitive RNA-dependent RNA polymerases.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed* (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed_" (See *Vas-Cath* at page 1116). As there is no disclosure of the polynucleotides, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

The limited information provided in the specification is not deemed sufficient to reasonably convey to one skilled in the art that Applicants were in possession of the broadly claimed polynucleotides at the time the application was filed. Thus it is concluded that the written description provision of 35 U.S.C 112, first paragraph, is not satisfied for the claimed polynucleotides. Applicants are reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C 112 is severable from its enablement provision (see page 1115).

Enablement

Applicant's amendments requiring in vitro delivery of the recited compositions is sufficient to overcome the portion of the rejection related to *in vivo* uses of the invention. However, the rejection is maintained because the specification, while being enabling for a DNA molecule encoding the Sindbis virus non-cytopathic, temperature-sensitive replicase with P726S NSP2 and G153E NSP4 mutations encoded by SEQ ID NO:1, does not reasonably provide enablement for DNA molecules encoding any other alphaviral non-cytopathic, temperature-sensitive replicase.

Applicant argues that one need not be able to predict structure function relationships in order to enable the full scope of the claims because one could make the invention by screening libraries of random or site-directed mutants for the appropriate characteristics. Applicant argues that complex experimentation is not necessarily undue, and points to *In re Wands* wherein the court found that screening large numbers of hybridomas to find a given antibody is not undue experimentation.

This is unpersuasive because the hybridoma art is non-analogous to the art of enzyme structure and function. A more precise analogy would be where one screened for a monoclonal antibody with catalytic function that was temperature sensitive. Applicant has presented no evidence that such an undertaking was routine in the art at the time of filing. In view of the unpredictability of polypeptide structure-function relationships, the failure of the specification to teach how to predict which mutations will give the desired characteristics, and the failure to

disclose more than one example of a Sindbis virus temperature sensitive, non-cytopathic replicase, one of skill in the art could not make or use the invention commensurate in scope with the claims.

JAMES KETTER
PRIMARY EXAMINER